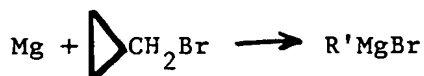


Declaration

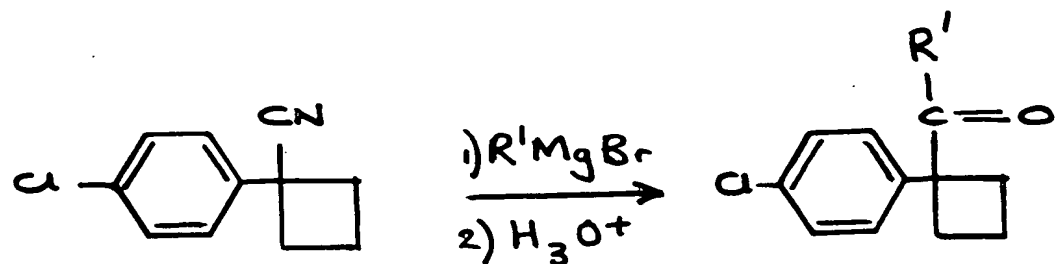
I, James Edward Jeffery, a British subject of 81 Greenland Crescent, Chilwell, Nottingham, England, do hereby declare that:-

- 1) In 1968 I attained Graduate Membership of the Royal Institute of Chemistry by examination and in 1971 I completed a period of research in the field of organic chemistry at University of Manchester Institute of Science and Technology which led to the award of a degree of Doctor of Philosophy in 1972.
- 2) I joined The Boots Company as a Research Chemist in 1971. In 1978 I was promoted to the post of Team Leader responsible for the synthesis of compounds which were to be tested as potential antidepressants. In 1981 I was appointed to the post of Section Leader and supervised the work of several chemists who were engaged in the preparation of compounds which were prepared as potential therapeutic agents for the treatment of mental illnesses including depression.
- 3) I am one of the inventors of the above identified US Patent Application.
- 4) Examples 10(u) and 11(g) of the specification of the above identified US Patent Application describe compounds in which R<sub>1</sub> in Formula I is defined as cyclopropylmethyl. These compounds were prepared in 1981 by the following synthetic procedure which is similar to the procedure which had been used previously to prepare the other compounds described in Examples 10 and 11. The procedure used was:-

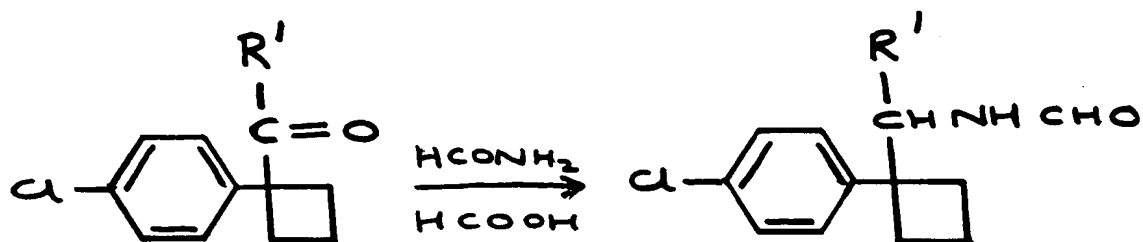
- i) preparation of a Grignard reagent by the reaction of cyclopropylmethyl bromide with magnesium



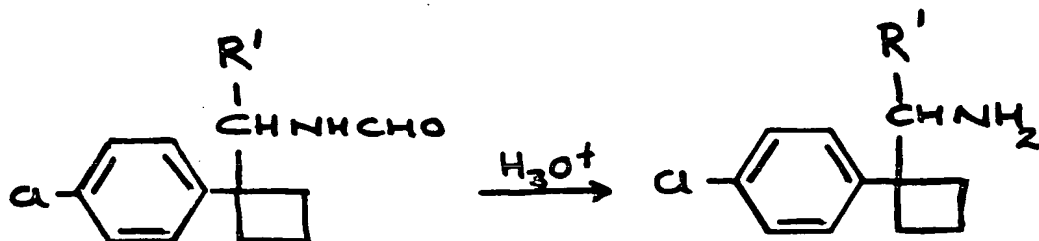
- ii) reaction of that Grignard reagent with 1-(4-chlorophenyl)-1-cyclobutanecarbonitrile followed by hydrolysis to give a ketone



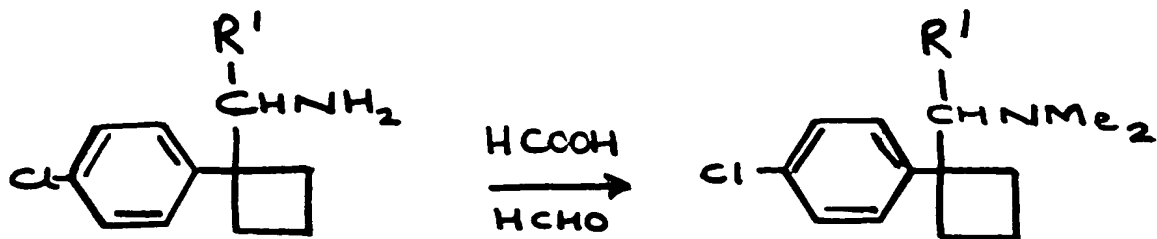
iii) reaction of the ketone with formamide and formic acid to give an N-substituted formamide



iv) acid hydrolysis of the N-substituted formamide compound to give a primary amine which was converted into a hydrochloride salt (Example 10u)



v) reaction of the primary amine with formic acid and formaldehyde to give a tertiary amine which was converted into a hydrochloride salt (Example 11g)



Elemental analyses and infra-red spectra were obtained for the compounds of Examples 10(u) and 11(g) and the compounds were assigned a structure in which R' was believed to be cyclopropylmethyl on the assumption that the Grignard reagent used in stage (i) of the procedure set out above was cyclopropylmethylmagnesium bromide.

5) The validity of this assumption was brought into question when I became aware during 1984 of a paper (Appendix I) by D.J. Patel, C.L. Hamilton and J.D. Roberts in J.Amer.Chem.Soc. 87 pp 5144-5148 1965 in which they reported that the Grignard reagent prepared from cyclopropylmethyl bromide was predominantly 3-butenylmagnesium bromide rather than the expected cyclopropylmethylmagnesium bromide. It therefore seemed possible that R' in the above reaction scheme was not cyclopropylmethyl as had been originally assumed but was in fact 3-butenyl. I therefore requested that proton magnetic resonance spectra be obtained on the compounds of Examples 10(u) and 11(g). The proton magnetic resonance spectra reported in the Declaration of Dr. Haran of even date did not reveal the presence of a cyclopropyl ring but did reveal the presence of a  $-\text{CH}=\text{CH}_2$  group. As a result of this information I concluded that the compounds of Examples 10(u) and 11(g) were compounds of formula I in which R<sub>1</sub> was 3-butenyl and not cyclopropylmethyl as originally thought.

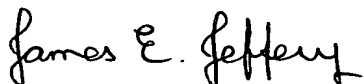
6) In February 1986, a proton nuclear magnetic resonance spectrum was obtained on the ketone which was produced in stage (ii) of the procedure outlined above to prepare the compounds of Example 10(u) and 11(g). As is reported in Dr. Haran's Declaration the spectrum showed that the ketone did not contain a cyclopropyl ring. The proton magnetic resonance spectrum was performed on a sample of the ketone which had been prepared in 1981. The sample of the ketone on which the proton magnetic resonance spectrum was performed was re-examined in 1986 by infra-red spectroscopy and by gas-liquid chromatography which confirmed that no

structural change had occurred to the sample on storage between 1981 when it was synthesised and 1986 when its proton magnetic resonance spectrum was taken.

7) Proton nuclear magnetic resonance spectroscopy has shown that R' in the ketone produced in stage (ii), in the primary amine produced in stage (iv) and in the tertiary amine produced in stage (v) of the procedure outlined in paragraph 4 above was not a group which contained a cyclopropyl ring. The structures of the compounds of Examples 10(u) and 11(g) as set out in the specification filed with the above identified patent application were therefore incorrect. I concluded that the correct structure of R' in these compounds was 3-butenyl which is consistent with the work reported by Patel et al reported in (5) above and the nuclear magnetic resonance spectra reported in Dr. Haran's Declaration. So that the structures are correctly identified in the specification it would be necessary to replace "cyclopropylmethyl" by "3-butenyl" in Example 10(u) on page 33 line 9 and in Example 11(g) on page 34 line 24.

Further declarant sayeth not

I, the undersigned declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such wilful false statements may jeopardise the validity of the application or any patent issuing thereon.



James Edward Jeffery

Signed at Nottingham, England on the ~~24th~~ day of March 1987.